

Application No. 10/014,665  
Atty. Dock t No. 033218-018

### **REMARKS**

Claims 1-20 and 22-32 are pending in the present application. Claim 18 was rejected under 35 U.S.C. § 112, claim 21 was rejected under 35 U.S.C. § 102, and claims 6-14 and 20 were rejected under 35 U.S.C. § 103. Claims 1-5, 15-17, and 19 have been allowed. Claim 21 has been cancelled. New claims 22-32 have been added. Support for claims 22-32 is found in the application at least in paragraph number 0021 on pages 6-7. Reexamination of the application and reconsideration of the rejections are respectfully requested in view of the above amendments and the following remarks, which follow the order set forth in the Office Action.

#### ***A. Claim Rejections - 35 U.S.C. § 112***

Claim 18 was rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Examiner indicated that claim 18 is improperly dependent on claim 15. Applicants respectfully traverse this rejection.

Claim 18 properly depends from independent claim 15. Claim 15 recites a process for the production of oxandrolone comprising the steps of:

(a) reacting mestanolone with IBX to form 17 $\beta$ -hydroxy-17 $\alpha$ -methyl-5 $\alpha$ -androst-1-en-3-one;

(b) reacting the 17 $\beta$ -hydroxy-17 $\alpha$ -methyl-5 $\alpha$ -androst-1-en-3-one with osmium tetroxide and N-methylmorpholine N-oxide to form 1 $\alpha$ , 2 $\alpha$ , 17 $\beta$ -trihydroxy-17 $\alpha$ -methylandrostan-3-one;

(c) reacting the 1 $\alpha$ , 2 $\alpha$ , 17 $\beta$ -trihydroxy-17 $\alpha$ -methylandrostan-3-one with sodium metaperiodate to form 17 $\beta$ -hydroxy-17 $\alpha$ -methyl-1-oxo-1,2,-seco-A-nor-5 $\alpha$ -androstan-2-oic acid;

(d) forming oxandrolone from the 17 $\beta$ -hydroxy-17 $\alpha$ -methyl-1-oxo-1,2,-seco-A-nor-5 $\alpha$ -androstan-2-oic acid by reacting th 17 $\beta$ -hydroxy-17 $\alpha$ -methyl-1-oxo-1,2,-s co-A-nor-5 $\alpha$ -

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androstan-2-oic acid with sodium borohydride followed by an acid treatment comprising addition of hydrochloric acid.

Claim 18 recites the process of claim 15 wherein the process is performed without the use of lead tetraacetate.

Applicants believe that claim 18 is definite and is properly dependent upon independent claim 15. Therefore, Applicants respectfully request that the rejection be withdrawn.

***B. Claim Rejections - 35 U.S.C. § 102***

Claim 21 was rejected under 35 U.S.C. § 102(b) as being anticipated by Bi et al. (DN 117:151203, CAPLUS, abstract of Steroids (1992), 57(7), 306-12) and Masse et al. (J. Chromatogr. 1989). However, the rejection over Masse et al. (J. Chromatogr. 1989) was withdrawn in a telephone conversation with the Examiner on September 19, 2002. As claim 21 has been cancelled, the remaining rejection over Bi et al. is now moot.

***C. Claim Rejections - 35 U.S.C. § 103***

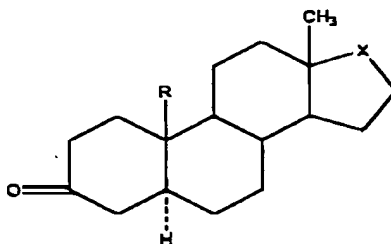
Claims 6-14 and 20 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Jung et al. (U.S. Patent No. 3,246,014). However, in a telephone conversation with the Examiner on December 2, 2002, the Examiner indicated that Jung et al. was mistakenly cited rather than the intended reference, which is Pappo (U.S. Patent No. 3,128,283). Applicants thank the Examiner for clarifying the rejection.

Pappo (U.S. Patent No. 3,128,283) discloses 17-oxygenated androstane and estrane derivatives in which the A ring contains a lactone structure. Pappo discloses that suitable starting materials for the manufacture of lactones of the androstane series with a -CR'H- radical at position 1 are 17-oxygenated androst-4-en-3-ones and 17-oxygenated androsta-1,4-dien-3-ones, wherein the member at position 17 is a carbonyl,  $\beta$ -hydroxymethylene, or  $\alpha$ -(lower alkyl)- $\beta$ -hydroxymethylene radical. Pappo discloses that reacting the latter compounds with a mixture of osmium tetroxide and lead tetraacetate results in cleavage of the 1,2-double bond to produce 1,2-substituted androstane compounds, and states that instead of lead tetraacetate, other similar reagents

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such as sodium periodate or potassium chlorate can be used. Pappo further discloses a specific example where 17 $\beta$ -hydroxy-17 $\alpha$ -methyl-5 $\alpha$ -androst-1-en-3-one in aqueous acetic acid is reacted with osmium tetroxide and lead tetracetate to afford 17 $\beta$ -hydroxy-17 $\alpha$ -methyl-1-oxo-1,2,-seco-A-nor-5 $\alpha$ -androstan-2-oic acid, which is converted to 17 $\beta$ -hydroxy-17 $\alpha$ -methyl-2-oxa-5 $\alpha$ -androstan-3-one (oxandrolone) by reduction with sodium borohydride in aqueous sodium hydroxide. (See column 2, line 43-column 3, line 41; see also Example 5 at column 9, line 48-column 10, line 29).

In addition, Pappo states that A-ring saturated lactones with an ethylene group at position 1 are obtained by a process utilizing as starting materials compounds of the structural formula



wherein R is a hydrogen or a methyl radical and X is  $\beta$ -hydroxymethylene or  $\alpha$ -(lower alkyl)- $\beta$ -hydroxymethylene. Pappo discloses that reaction of these substances with isopropenyl acetate affords the corresponding 3-enol acetate, which is treated with ozone, then with zinc dust, and finally with sodium hydroxide to afford the intermediate 17-oxygenated-2-oxo-2,3-seco-3-oic acids, which are reduced with sodium borohydride in aqueous sodium hydroxide to afford the corresponding 2-hydroxy-3-oic acid. The acid is cyclized by heating at an elevated temperature in a suitable inert solvent to afford 3-oxa-4-ones. Pappo teaches that these processes are exemplified by the use of 17 $\beta$ -hydroxy-17 $\alpha$ -methyl-5 $\alpha$ -androstan-3-one (i.e., mestanolone) to produce a final product of 17 $\beta$ -hydroxy-17 $\alpha$ -methyl-3-oxa-A-homo-5 $\alpha$ -androstan-4-one. The first step of this specific process is reacting 17 $\beta$ -hydroxy-17 $\alpha$ -methyl-5 $\alpha$ -androstan-3-one (i.e., mestanolone) with isopropenyl acetate and p-toluenesulfonic acid to afford 17 $\alpha$ -methyl-5 $\alpha$ -androst-2-ene-3,17 $\beta$ -diol 3,17-diacetate. (See column 4, line 41-column 5, line 2; see also Example 30 at column 16, line 30-column 17, line 23).

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In contrast, independent claim 6 of the present application recites a process for the production of oxandrolone comprising the steps of:

- (a) oxidizing mestanolone to form 17 $\beta$ -hydroxy-17 $\alpha$ -methyl-5 $\alpha$ -androst-1-en-3-one;
- (b) hydroxylating the 17 $\beta$ -hydroxy-17 $\alpha$ -methyl-5 $\alpha$ -androst-1-en-3-one to form 1 $\alpha$ , 2 $\alpha$ , 17 $\beta$ -trihydroxy-17 $\alpha$ -methylandrostan-3-one;
- (c) cleaving the 1 $\alpha$ , 2 $\alpha$ , 17 $\beta$ -trihydroxy-17 $\alpha$ -methylandrostan-3-one to form 17 $\beta$ -hydroxy-17 $\alpha$ -methyl-1-oxo-1,2,-seco-A-nor-5 $\alpha$ -androstan-2-oic acid; and
- (d) reducing the 17 $\beta$ -hydroxy-17 $\alpha$ -methyl-1-oxo-1,2,-seco-A-nor-5 $\alpha$ -androstan-2-oic acid to form oxandrolone.

Independent claim 20 recites a similar process for the production of oxandrolone, but recites that the mestanolone is oxidized using IBX and recites that at least two by-products are formed in step (a) that are non-reactive to steps (b) and (c).

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference. Second, there must be a reasonable expectation of success. Finally, the prior art reference must teach or suggest all the claim limitations. See, e.g., MPEP § 2143. Thus, to support a conclusion of obviousness, the prior art must suggest the desirability of making the claimed invention, i.e., provide a teaching or suggestion to one of ordinary skill in the art to have made the changes that would have produced the claimed subject matter. (*Ryco Mfg. Co. v. Nu-Star, Inc.*, 950 F.2d 714, 718 (Fed. Cir. 1991)). These requirements have not been met.

Pappo does not teach all of the claim limitations of independent claim 6 or independent claim 20. For example, Pappo does not teach or suggest step (a) of independent claim 6 or step (a) of independent claim 20. That is, Pappo does not teach or suggest oxidizing mestanolone to form 17 $\beta$ -hydroxy-17 $\alpha$ -methyl-5 $\alpha$ -androst-1-en-3-one (claim 6) or oxidizing mestanolone using IBX to form 17 $\beta$ -hydroxy-17 $\alpha$ -methyl-5 $\alpha$ -androst-1-en-3-on (claim 20).

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Applicants disagree with the Examiner's assertion that Pappo teaches oxidizing mestanolone by osmium tetroxide with lead tetracetate in acidic condition. Pappo teaches reacting 17 $\beta$ -hydroxy-17 $\alpha$ -methyl-5 $\alpha$ -androst-1-en-3-one in aqueous acetic acid with osmium tetroxide and lead tetracetate to afford 17 $\beta$ -hydroxy-17 $\alpha$ -methyl-1-oxo-1,2,-seco-A-nor-5 $\alpha$ -androstan-2-oic acid, which is then converted to 17 $\beta$ -hydroxy-17 $\alpha$ -methyl-2-oxa-5 $\alpha$ -androstan-3-one (oxandrolone) by reduction with sodium borohydride in aqueous sodium hydroxide. Pappo also teaches a process using 17 $\beta$ -hydroxy-17 $\alpha$ -methyl-5 $\alpha$ -androstan-3-one (i.e., mestanolone) as a starting material to produce a final product of 17 $\beta$ -hydroxy-17 $\alpha$ -methyl-3-oxa-A-homo-5 $\alpha$ -androstan-4-one, the first step of which is to react 17 $\beta$ -hydroxy-17 $\alpha$ -methyl-5 $\alpha$ -androstan-3-one (i.e., mestanolone) with isopropenyl acetate and p-toluenesulfonic acid to afford 17 $\alpha$ -methyl-5 $\alpha$ -androst-2-ene-3,17 $\beta$ -diol 3,17-diacetate. Pappo does not teach oxidizing mestanolone by osmium tetroxide with lead tetracetate in acidic condition as asserted by the Examiner. Moreover, Pappo does not teach or suggest step (a) of claim 6 or step (a) of claim 20.

Furthermore, there is no suggestion or motivation to modify Pappo to achieve the claimed invention. "Even when obviousness is based on a single prior art reference, there must be a showing of a suggestion or motivation to modify the teachings of that reference." *In re Kotzab*, 55 U.S.P.Q.2d 1313, 1316-17 (Fed. Cir. 2000). No suggestion or motivation has been provided to modify Pappo to provide a process for the production of oxandrolone as recited in independent claim 6 or independent claim 20. As discussed above, Pappo teaches that suitable starting materials to produce lactones of the androstane series with a -CR'H- radical at position 1 are 17-oxygenated androst-4-en-3-ones and 17-oxygenated androsta-1,4-dien-3-ones, and teaches production of oxandrolone beginning with 17 $\beta$ -hydroxy-17 $\alpha$ -methyl-5 $\alpha$ -androst-1-en-3-one. Mestanolone is not named or suggested as a starting material in the process taught for making oxandrolone. To the contrary, also as discussed above, Pappo teaches that A-ring saturated lactones with an ethylene group at position 1 (which do not include oxandrolone) are obtained by a process utilizing a starting material such as 17 $\beta$ -hydroxy-17 $\alpha$ -methyl-5 $\alpha$ -androstan-3-one (i.e., mestanolone). There is no suggestion or motivation to

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modify Pappo to provide the process recited in claim 6, wherein mestanolone is oxidized to form 17 $\beta$ -hydroxy-17 $\alpha$ -methyl-5 $\alpha$ -androst-1-en-3-one or to provide the process of claim 20, wherein mestanolone is oxidized using IBX to form 17 $\beta$ -hydroxy-17 $\alpha$ -methyl-5 $\alpha$ -androst-1-en-3-one.

Therefore, claims 6-14 and 20 are not obvious over Pappo because (1) the cited art does not teach all the limitations of independent claims 6 or 20 and (2) there is no motivation to modify Pappo to achieve the claimed invention. Applicants respectfully request that the Examiner withdraw the 35 U.S.C. § 103 rejections of these claims.

### Conclusion

For the foregoing reasons, the pending claims are considered allowable. A Notice to this effect is respectfully solicited. If any questions remain, the Examiner is invited to contact the undersigned attorney at the number given below.

Respectfully submitted,

BURNS, DOANE, SWECKER & MATHIS, L.L.P.

By: Joshua T. Elliott  
Joshua T. Elliott  
Registration No. 43,603

P.O. Box 1404  
Alexandria, Virginia 22313-1404  
(919) 941-9240

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